REMARKS

I. Statement of the Interview

The Applicants' representative, Christian M. Bauer, appreciates the Examiner's time in conducting the in-person interview on 11 January 2008. Discussions focused on the cited prior art, namely US 6,316,029 (specifically Example 3) and EP 0 719 549 (specifically whether turbidity correlates to a particle size distribution). Also discussed were the possibility of amending claim 1 to recite a specific embodiment of an amount of gel forming substance as recited in claim 4 and/or amending claim 1 to recite a specific embodiment of the gel forming substance as recited in claim 8. Applicants accept the Examiner's Interview Summary mailed January 15, 2008.

II. Status of the claims

Claims 1-8, 12-22, 24-28, 30-43, and 47 are pending. Claims 1, 4, 14, 15, 22, 31, 32, and 47 are amended for clarity.

Previous claim 1 recited "wherein the gel forming substance forms a matrix surrounding the nanoparticulate active agent particles and surface stabilizer." Applicants clarified this requirement by amending the claim to read "a gel matrix of at least one gel forming substance." Previous claim 1 recited "gel forming substance, which exhibits gelation sufficient to retain excess water . . . wherein the pharmaceutical composition comprises from about 20% to about 97% water, based on the total weight of the composition." Applicants clarified this requirement by amending the claim to read "the gel forming substance in an amount which exhibits gelation sufficient to retain water in an amount of from about 20% to about 97%, based on the total weight of the composition."

Claim 4 was amended to clarify the calculation of weight percent of the gel forming substance based upon the total weight of the composition.

Claim 14 was amended to clarify antecedent basis.

Claims 31 and 32 were amended to clarify that the "less" adjective was intended to convey that the time to reach T_{max} was less.

Claim 47 was amended consistent with the changes to claim 1.

No new matter has been added.

Although discussed during the interview, Applicants have not amended claim 1 to incorporate one of the specific embodiments listed claims 4 and/or 8, which claims have been consistently rejected during prosecution. Nothing in the prosecution history indicates that such amendments would otherwise change the Examiner's position.

Applicants submit herewith the excerpt of the *Handbook of Pharmaceutical Excipients, Fourth Edition* in an Information Disclosure Statement, as requested by the Examiner.

III. Rejections Under 35 U.S.C. § 102

Claims 1-8, 12-22, 24-28, 30-43 and 47 stand rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by U.S. Patent No. 6,316,029 to Jain et al. ("Jain") and by EP 0 719 549 ("EP 549"). Applicants respectfully traverse.

A. Jain does not teach nor reasonably suggest the claimed invention

The 19 Oct. 2007 Office Action concludes that Example 3 (Col. 14, lines 4-44) of Jain teaches each and every limitation of the claimed invention. Example 3 spray dries 200.0 g of a dispersion consisting of 30% drug, 3% PVP, and 0.15% SLS with 150.0 g of fluidized spray-dried mannitol in a fluidized bed granulator to form granules. After spray-drying, 20 g of water was passed through the feeding tube of the fluidized bed granulator and sprayed on the granules. At the end of spraying, the granules were dried by fluidizing for 5-7 minutes and harvested, yielding 186.7 g of granules. The granules were dry-blended with magnesium stearate and compressed to form tablets.

The Office Action acknowledges "the final, dry composition of Jain does not read on the instant claims." 19 Oct. 2007 Office Action at page 3. The Office Action, however, maintains the rejection concluding that the intermediate composition "which is obtained after

spraying with water but prior to drying anticipates the claimed composition." Id. The intermediate composition, according to the Office Action, is the granules that have been sprayed with 20 g of water ("wet granules"). Like the final tablet dosage form, the intermediate wet granules of Example 3 do not expressly, inherently, or even reasonably suggest the invention of claim 1.

Clarified claim 1 requires a solid or semi-solid pharmaceutical composition to have a gel matrix of at least one gel forming substance where the gel forming substance is in an amount which exhibits gelation sufficient to retain water in an amount of from about 20% to about 97%, based on the total weight of the composition.

First, there is nothing in the disclosure of Example 3 that teaches or reasonably suggests that the wet granules are composed of a gel matrix. Without a teaching of a gel matrix, the wet granules of Example 3 also fail to exhibit gelation sufficient to retain water in an amount of from about 20% to about 97%.

Second, there can be no conclusion drawn from Example 3 as to the water content of the wet granules. Claim 1 requires the water to be retained by the gel forming substance. Even if PVP is considered a gel-forming substance, Example 3 is silent with respect to whether the PVP is retaining any of the 20 g of sprayed water. Not only is Example 3 silent, but also one of ordinary skill in the art would understand Jain to teach that PVP is functioning as a surface stabilizer, not as a gelatin agent that retains water. See the passage beginning at Col. 7, line 15. Jain teaches that the function of a surface stabilizer is to physically adhere to the surface of the active agent but does not chemically bond to or interact with the agent. Col. 7, lines 19 and 20. There is nothing in Jain that teaches or reasonably suggests that PVP functions other than what is taught by Jain. That is, there is nothing in Jain that teaches PVP forms a gel matrix to retain water, let alone the amount of water claimed in claim 1. The fact that Applicants specification discloses the use of PVP as a gel forming substance is not germane to what one of ordinary skill in the art would understand about PVP from reading Jain.

Third, any assumption that the wet granules will have the claimed water content at the point at which they are sprayed with the 20 g of water is unsupported by technical reasoning

or knowledge of one skilled in the art. Even if the Office Action assumes the 20 g of water is completely absorbed into the granule, with the information given in Example 3, the wet granule would still not have the claimed water content. Example 3 describes 20 g of water being sprayed on a mixture of 200 g ketoprofen and 150 g mannitol. If it is assumed that all 20 g of water is absorbed, the amount of water would be only 5.4 % (20/(200+150+20)). After subsequent processing, these granules were dried and screened with a #35 sieve, resulting in a final yield of 186.7 g. Even if these granules contained all of the 20 g water applied, the water content would only be 11% (20/186.7). Therefore, Jain fails to teach an element of the claims, and therefore cannot anticipate.

Furthermore, Applicants note that, unlike the claim requirement of a gel matrix retaining the water, there is nothing in Example 3 that teaches how the water is absorbed into the granule. Water collecting on the surface of the granules would not read on the claimed requirement of a gel forming substance in an amount which exhibits gelation sufficient to retain water. Therefore, Jain fails to teach or enable this element of the claims.

For at least the above reasons, Jain does not support the anticipation of the pending claims. Withdrawal of the rejection is respectfully requested.

B. A measurement of turbidity does not correlate to a particle size distribution having an affective average particle size of less than 2000 nm

The 19 Oct. 2007 Office Action concludes that EP 0 719 549 anticipates the claimed invention. Specifically, the Office Action states "although the particle size is not discussed [in EP 549] the particle size is understood to be much less than 2000 nm. If the particle size were greater, higher turbidity would necessarily result." These statements are incorrect, and Applicants respectfully traverse the rejection.

Turbidity is defined by the American Public Health Association as an expression of the optical property that causes light to be scattered and absorbed rather than transmitted in straight lines. See page 4, second paragraph of *Turbidity Science*, Technical Information Series – Booklet No. 11, Michael J. Sadar, Hach Company 1998, copy enclosed. The reference can also be found at http://www.hach.com/fmmimghach?/CODE:L7061549|1. Accordingly, turbidity is not a direct measure of suspended particles in water but, instead, a

measure of the scattering effect such particles have on light. *Id.* The manner in which the sample interferes with light transmittance is related to the size, shape, and composition of the particles in the solution and the wavelength of the incident light. *Id.* In other words, turbidity refers to the clarity of a fluid.

EP 549 at page 4, lines 41-44 measures the turbidity of the samples using a Hach Ratio/XR Turbidimeter. The enclosed reference, *Turbidity Science*, is a publication by the Hach Company that manufactures similar (albeit most likely different model) turbidimeters as used in EP 549. (EP 549 does not provide a model number for the Ratio/XR turbidimeter used.) Pages 16-19 of *Turbidity Science* explains in detail the design objectives, optical design, and electronic design of Ratio/XR Turbidimeters. Specifically, at page 17, 2nd paragraph, 1st sentence, the reference states "[Ratio/XR] turbidimeters operate on the principle that the amount of light scattered from a sample is proportional to the *quantity* of particulate matter in that sample." Emphasis Added.

Turning now to EP 549, nowhere in EP 549 is there described a correlation between the turbidity values given and the number of particles in the sample, let alone identifying which samples had an effective average particle size of less than 2000 nm. In addition, one of ordinary skill in the art could not draw any meaningful conclusions as to the particle size of particles in the samples of EP 549.

In order to correlate a particle size and/or size distribution from a turbidity measurement, at minimum, two the following data points would be required: 1) a reference sample of known particle concentration and its turbidity measurement, 2) the size distribution of the particles within the reference sample, and 3) the optical properties of the all components within the reference sample and tested samples.

EP 549 fails to provide any of these data points, which is not surprising as EP 549 is concerned with the clarity of the resulting gelled product, not the size distribution of any particles that did not dissolve within the gelled sample. First, EP 549 does not provide a reference sample of measured turbidity and of known particle size. Second, EP 549 does not provide a reference of measured turbidity and of known particle size distribution. The Office Action at Page 4 acknowledges these first two points. Finally, EP 549 does not discuss the

optical properties of all the components within its sample, i.e., the PEGs, sodium acetate, sodium stearate, Poloxomer, acetaminophen, etc. Without two of these data points, one of ordinary skill in the art cannot make a conclusion from a turbidity value whether or not the sample has an effective average particle size of less than 2000 nm as is claimed.

Applicants further comment on the following statement in the Office Action: "If the particle size were greater, higher turbidity would necessarily result." This is also not true. As discussed above, turbidity is a measurement of the scattering of light by particles. As the particle sizes increase, the void spaces between the particles becomes larger. The result is that light passes through these larger void spaces, is not scattered, and the resulting turbidity measurement decreases. Therefore, a statement that if particle size were greater, higher turbidity would necessarily result is not accurate. A more accurate statement is that when the *number* of particles increases, the turbidity measurement increases. The number of particles, however, is not indicative of their size.

Accordingly, with the explanation of the turbidimeter used in EP 549 as evidenced by the *Turbidity Science* reference, the Office Action conclusion that the particle size is understood to be much less than 2000 nm based solely upon the reported turbidity measurements in EP 549 is in error. For at least the above reasons, EP 549 cannot be used to support the anticipation rejection. Withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully believe that all rejections have been rendered moot, accommodated, or overcome. Applicants respectfully request that the Examiner reconsider and withdraw the present rejections, and allow the pending claims. As Applicants believe that the pending claims are in condition for allowance, Applicants also request that the Examiner rejoin and examine the withdrawn claims.

If it is believed that telephone communication can expedite the prosecution of this application, the Examiner is invited to contact the undersigned at the number below.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date Jan 22, 2008

By _____
Michele M. Simkin
Attorney for Applicants
Registration No. 34,717

FOLEY & LARDNER LLP
Customer Number: 31049
Telephone: (202) 672-5538
Facsimile: (202) 672-5399